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Asymmetric Synthesis of (−)-Indolizidines 167B and 209D Based on Stereocontrolled Allylation of a Chiral Tricyclic *N*-Acyl-*N,O*-acetal

Naoki Yamazaki, Toshimasa Ito, and Chihiro Kibayashi*

School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

kibayasi@ps.toyaku.ac.jp

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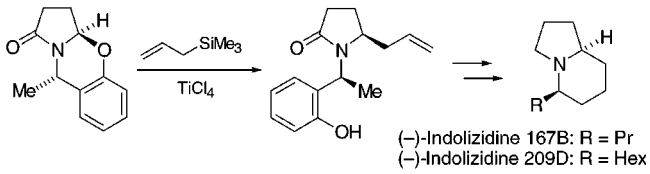
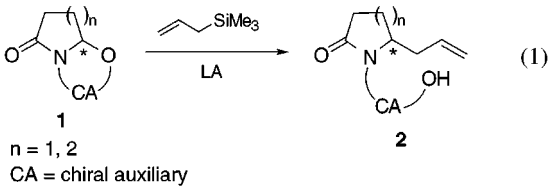
ABSTRACT



The tricyclic *N*-acyl-*N,O*-acetal incorporating (*S*)-2-(1-aminoethyl)phenol as a chiral auxiliary underwent $TiCl_4$-mediated allylation to give the chiral (5*S*)-allylpyrrolidinone with retention of configuration in high yield and diastereoselectivity. On the bases of this methodology, the asymmetric syntheses of the dendrobatid alkaloids (−)-indolizidines 167B and 209D were achieved.

Bicyclic lactams incorporating chiral cyclic *N,O*-acetals **1** have been the subject of current interest due to their potential use in asymmetric synthesis.[1] In this context, Meyers[2] has demonstrated the utility of **1** ($n = 1$) in the asymmetric synthesis of 2-substituted pyrrolidines involving the use of diastereoselective Lewis acid-mediated allylation, which has subsequently been applied to the asymmetric preparation of 2-substituted piperidines (eq 1).[3] In these investigations, the



(1)

amino acid-derived amino alcohols such as phenylglycinol, alaninol, valinol, and *tert*-leucinol proved to be effective chiral auxiliaries that allowed for the successful implementation of asymmetric induction. However, N-dealkylation of **2** to yield the corresponding N-nor compounds requires the use of phenylglycinol as the only auxiliary capable of allowing the cleavage of the *N*-benzyl group under the reductive conditions, which seems to limit the utility of this asymmetric protocol.

We recently demonstrated[4] that 2-(1-aminoethyl)phenol (**5**) is a notably effective chiral auxiliary for the tricyclic *N,O*-acetal-based allylation, leading to higher reactivity and selectivity (compared with the amino alcohols employed) in the formation of a chiral piperidinone; the higher reactivity can be attributed to the fact that phenoxide ions are much better leaving groups than alkoxide ions in nucleophilic displacement reactions. In this paper, we report the extension of this allylation reaction using the chiral aminophenol auxiliary (*S*)-**5** to the asymmetric synthesis of a 5-substituted pyrrolidinone and the application of this methodology to the enantioselective synthesis of simple dendrobatid alkaloids,

(1) For a recent review, see: Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503.
(2) (a) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc*. **1991**, *113*, 9858. (b) Meyers, A. I.; Burgess, L. E. *J. Org. Chem*. **1991**, *56*, 2294.
(3) Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett*. **1994**, *35*, 2223.
(4) (a) Yamazaki, N.; Ito, T.; Kibayashi, C. *Synlett* **1999**, 37. (b) Yamazaki, N.; Ito, T.; Kibayashi, C. *Tetrahedron Lett*. **1999**, *40*, 739.

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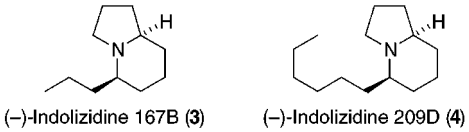
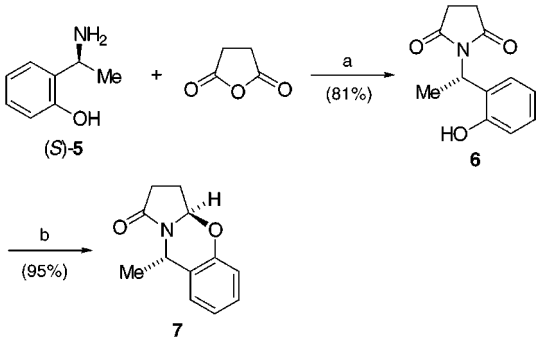
(−)-indolizidines 167B (**3**)[5] and 209D (**4**)[6] bearing a single substituent at C(5).[7]



The requisite chiral tricyclic *N*-acyl-*N*,*O*-acetal **7** was prepared by the sequence given in Scheme 1. Condensation

Scheme 1[a]

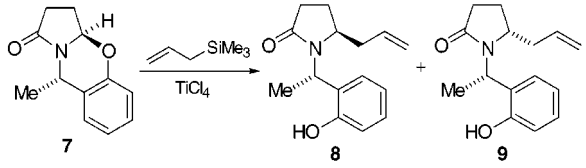


[a] (a) Benzene, reflux, then AcCl, reflux; (b) Red-Al, then HCl.

of succinic anhydride (1.2 equiv) with (*S*)-2-(1-aminoethyl)-phenol [(*S*)-**5**] (reflux in benzene and then reflux with AcCl) gave the corresponding imide **6** (81%). Partial reduction of **6** with Red-Al and subsequent acid treatment of the resulting 5-hydroxylactam allowed formation of the *N*,*O*-acetal **7** as a single isomer in 95% yield. The relative stereochemistry of hydrogen at C(3a) in **7** was confirmed by NMR NOE experiments which showed interaction between the hydrogen at C(3a) and the C(9)-methyl.

We next examined the allylation of the chiral tricyclic *N*,*O*-acetal **7** by treatment with allyltrimethylsilane and titanium tetrachloride, and the results are summarized in Table 1. The

Table 1. Allylation of Tricyclic *N*-Acyl-*N*,*O*-acetal **7**[a]



entry	solvent	**8**/**9** ratio[b]	yield[c] (%)
1	CH_2Cl_2	3.1:1	95
2	chlorobenzene	3.9:1	99
3	benzene	6.3:1	91
4	toluene	7.2:1	90
5	ethylbenzene	8.0:1	93
6	*p*-xylene	8.7:1	92

[a] All reactions were carried out using allyltrimethylsilane (3 equiv) and $TiCl_4$ (3 equiv) at 40 °C. [b] Estimated by the ^{1}H NMR spectrum. [c] Isolated yield after chromatography.

results clearly demonstrated that these reactions proceed in high yield (>90%) and lead to the (5*S*)-allylated product **8** as a major diastereomer with retention of configuration at the reaction center. Because of difficulty of the stereochemical assignment of the products **8** and **9** based on NMR spectra, crystallization of these compounds was attempted for X-ray analysis, but it failed. However, recrystallization of racemic **9**, prepared using the racemic aminophenol (±)-**5** by the same reaction sequence as shown in Scheme 1 and then the allylation, provided crystals (mp 107−109 °C, from benzene) suitable for X-ray crystallography which allowed assignment of the relative stereochemistry of the two chiral centers as shown (Figure 1), thus leading to formal establishment of the absolute stereochemistry of chiral **8** and **9**. The

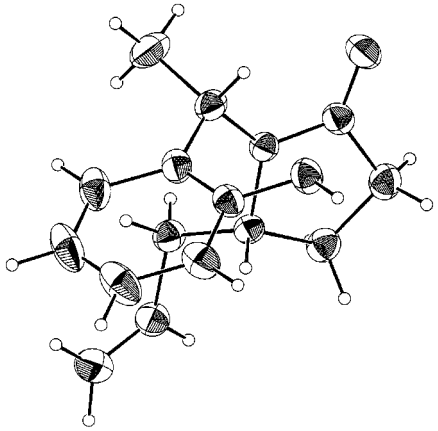


Figure 1. X-ray crystallographic structure of racemic **9** represented by one enantiomer.

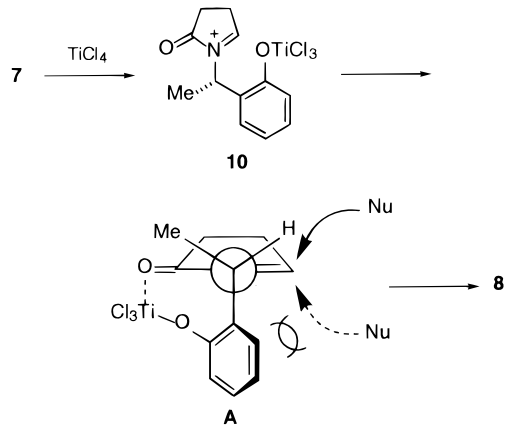
(5) For enantioselective syntheses of indolizidine 167B, see: (a) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. (b) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513. (c) Fleurant, A.; Célérier, J. P.; Lhommet, G. *Tetrahedron: Asymmetry* **1992**, *3*, 695. (d) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 3119. (e) Fleurant, A.; Saliou, C.; Célérier, J. P.; Platzer, N.; Moc, T. V.; Lhommet, G. *J. Heterocycl. Chem.* **1995**, *32*, 255. (f) Takahata, H.; Bandoh, H.; Momose, T. *Heterocycles* **1995**, *41*, 1797. (g) Lee, E.; Li, K. S. Lim, J. *Tetrahedron Lett.* **1996**, *37*, 1445. (h) Weymann, M.; Pfrengle, W.; Schollmeyer, D.; Kunz, H. *Synthesis* **1997**, 1151. (i) Angle, S. R.; Henry, R. M. *J. Org. Chem.* **1997**, *62*, 8549. (j) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C.; Canet, I. *Tetrahedron Lett.* **1999**, *40*, 1661. (k) Chênevert, R.; Ziarani, G. M.; Dasser, M. *Heterocycles* **1999**, *51*, 593.

(6) For enantioselective syntheses of indolizidine 209D, see: (a) Åhman, J.; Somfai, P. *Tetrahedron Lett.* **1995**, *36*, 303. Åhman, J.; Somfai, P. *Tetrahedron* **1995**, *51*, 9747. (b) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398. (c) Jefford, C. W.; Sienkiewicz, K. Thornton, S. R. *Helv. Chim. Acta* **1995**, *78*, 1511. (d) Takahata, H.; Kubota, M.; Ihara, K.; Okamoto, N.; Momose, T.; Azer, N.; Eldefrawi, A. T.; Eldefrawi, M. E. *Tetrahedron: Asymmetry* **1998**, *9*, 3289. See also refs 5a, 5d, and 5g.

(7) These indolizidine alkaloids 167B and 209D were detected once as a very minor trace components in unidentified dendrobatid frogs found in a single population [(a) Daly, J. W. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 205. (b) Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T. K.; Albuquerque, E. X. *Neurochem. Res.* **1986**, *11*, 1227]. Their structures have been tentatively assigned as **3** and **4** on the basis of mass spectral evidence whereas their absolute configurations were simply inferred as 5*R*,9*R* by analogy to the structurally related indolizidine 223AB whose absolute stereochemistry is known.

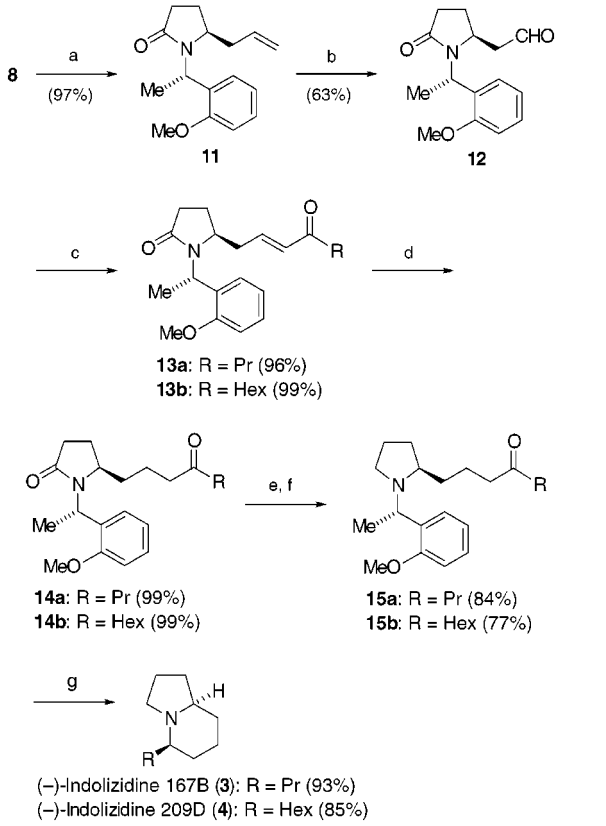
results summarized in Table 1 also demonstrated that the selectivity is significantly influenced by the solvent used. The reaction temperature of 40 °C proved to be optimal for the reaction: lower temperature (e.g., 20 °C) resulted in a very slow reaction, while higher temperature (50 °C) caused decomposition. Thus, the allylation using CH_2Cl_2 as a solvent at 40 °C afforded a mixture of **8** and **9** in a 3.1:1 ratio and 95% yield (entry 1). Changing the solvent from CH_2Cl_2 to chlorobenzene showed a small increase in diastereoselectivity (3.9:1, entry 2). The use of benzene and its alkyl derivatives such as toluene and ethylbenzene as solvents afforded significant improvements in the selectivity of up to 6.3:1, 7.2:1, and 8.0:1, respectively (entries 3−5), and when *p*-xylene was used, a much higher selectivity (8.7:1) was obtained (entry 6).

The preference of the retentive isomer **8** over the inversive isomer **9** in this allylation reaction is inconsistent with an S_N2 pathway and therefore is consistent with the reaction proceeding by an S_N1 process via the presumed intermediacy of an *N*-acyl iminium ion. Thus, the initially formed *N*-acyl iminium ion **10** is expected to adopt conformation **A** with the hydrogen atom in the inside position which minimizes the 1,3-allylic strain with the C═N bond. In this conformation, a coordination of the titanium(IV) phenoxide with the carbonyl oxygen atom is possible. In such a stereochemical arrangement, silane approach occurs from the face opposite the phenyl group to generate **8** with retention of configuration at the reaction center.



With the (5*S*)-allylated product **8** in hand, O-methylation afforded the methoxy derivative **11**, which underwent oxidative cleavage of the olefin moiety using OsO_4−$NaIO_4$ to give aldehyde **12** in 61% overall yield (Scheme 2). The Horner−Emmons olefination with the phosphonate [$(EtO)_2$P(O)CH_2C(O)Pr] provided (*E*)-enone **13a** as a single isomer, which was converted to propyl ketone **14a** by olefin hydrogenation in 95% overall yield. Reduction of **14a** with $LiAlH_4$, followed by Dess−Martin oxidation of the resulting amino alcohol, afforded amino ketone **15a** (84% yield for two steps). Upon catalytic hydrogenation of **15a** using palladium on carbon, hydrogenolytic cleavage of the *N*-benzyl moiety and subsequent intramolecular reductive amination occurred as a one-pot reaction to furnish (−)-indolizidine 167B (**3**) in 93% yield as a single isomer: $[\alpha]^{20}_D$ −119.1 (*c* 0.24, CH_2Cl_2) [lit.[5a] $[\alpha]^{20}_D$ −111.3 (*c* 1.3, CH_2Cl_2)]. The spectral data (^{1}H and ^{13}C NMR, and MS) of the synthetic material are identical to those reported[5a] for (5*R*,9*R*)-(−)-indolizidine 167B.

Scheme 2[a]



[a] (a) MeI, K_2CO_3 acetone; (b) OsO_4, $NaIO_4$, dioxane−H_2O (3:1); (c) $(EtO)_2P(O)CH_2C(O)R$, NaH, THF; (d) H_2, Pd−C, MeOH; (e) $LiAlH_4$, THF, reflux; (f) Dess−Martin periodinate, CH_2Cl_2; (g) H_2, Pd−C, MeOH.

The same reaction sequence starting from aldehyde **12** as that described above for (−)-indolizidine 167B was then applied to the synthesis of (−)-indolizidine 209D (**4**). Thus **12** was subjected to Horner−Emmons condensation with $(EtO)_2P(O)CH_2C(O)C_6H_{13}$ to give the single (*E*)-enone **13b** in 99% yield. Conversion of **13b** to **15b** was achieved through sequential hydrogenation, $LiAlH_4$ reduction, and Dess−Martin oxidation in 76% overall yield. Hydrogenation of **15b** exclusively provided (−)-indolizidine 209D (**4**), with spectral data (^{1}H and ^{13}C NMR, and MS) identical to those reported,[5a] in 85% yield: $[\alpha]^{20}_D$ −87.6 (*c* 0.45, CH_2Cl_2) [lit.[6d] $[\alpha]^{20}_D$ −89.64 (*c* 1.880, CH_2Cl_2)].

In conclusion, the tricyclic lactam incorporating a chiral cyclic *N*,*O*-acetal derived from (*S*)-2-(1-aminoethyl)phenol underwent $TiCl_4$-mediated allylation with allyltrimethylsilane to give the chiral (5*S*)-allylpyrrolidinone in high yield and diastereoselectivity. This methodology was successfully applied to the asymmetric syntheses of the dendrobatid alkaloids (−)-indolizidines 167B and 209D.

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